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Possible Etiologic Mechanisms in Chemical Carcinogenesis

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Some highlights in the development of our knowledge about carcinogens as etiological agents for cancer are reviewed briefly. Advances during the past 20 years relating to metabolic activation with the genesis of reactive metabolites, molecular targets and their interactions with activated carcinogens, oncogenes as molecular targets and the dependence on cell proliferation, all relating to the initiation process, are reviewed. Critical to initiation is the new phenotype in the initiated cell, known only in one instance, the rat liver, in which the characteristic change is one of resistance to many xenobiotic influences. The need for clonal expansion of initiated cells as essential for carcinogenic effects is discussed. Differential inhibition has been shown as a dominant mechanistic pattern in the liver. In other systems, the manner in which clonal expansion is achieved is not evident. The need for studies of the processes involved in carcinogenesis, as well as the agents, is emphasized, in view of the continuing validity of the cell concept as the key to integrating the increasingly large volume of data from the molecular with the biological.

Introduction

The past 20 years have seen a remarkable change in attitude on the part of the medical and scientific community and of the public concerning causal factors in cancer development. The dominant theme in the 1940s, often unstated, was that when someone developed cancer, it was somehow their fault or their family's fault. Today, the fault lies in the environment. This radical change in perception occurred in the 1960s, just about the time of organization of the National Institute of Environmental Health Sciences.

This change in perception occurred for many reasons, both scientific and sociological. Two major factors were the realizations that smoking was a major cause of cancer and other chronic diseases, as focused by the report of the Surgeon General's Advisory Committee on Smoking and Health (1964), and distinctive ethnic groups living in one country, such as Japan, left their patterns of cancer and other disease incidences behind when they migrated to the United States, and their children became more integrated into the new country. The children acquired the disease patterns characteristic of North America, not the country of origin of their parents and grandparents.

This emphasis on environment brought into focus the known major etiologic agents for cancer: viruses, chemicals, and radiation (Table 1). So far, quantitatively, chemicals, in the form of smoking and occupation, are related to 35 to 40% or so of cancers in the Western World. Whether the majority of the remaining 60 to 75% of cancers are also related to chemicals in the environment is unknown, even though many scientists have expressed their personal bias in favor of this likelihood.

Table 1. Etiological agents in cancer.

Agents that can be transcribed or translated
RNA viruses (retroviruses)
DNA viruses
Oncogenes
Agents that destroy or alter information in target cells
Chemicals
Combined initiators-promoters (most carcinogens)
Initiators
Promoters
Radiation
Other
Nongenotoxic carcinogens
Foreign inert material
Dietary deficiency of choline

Let us now look at mechanisms with emphasis on chemicals. It is now clear that in most if not all systems, chemicals, to be carcinogens, have to have at least two major effects in general. One is the ability to induce special changes in a few target cells that are largely irreversible. This initiation action involves usually 1 per 10^5 or 10^6 target cells (liver, skin?) (*1,2*). The second effect is the ability to cause the expansion by cell proliferation of the initiated cells, presumably as examples of clonal expansion. This promotion action usually takes place automatically after the initiation when large doses or multiple or continuous doses of carcinogen are used. However, it can be brought about by the use of the

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same carcinogen as for initiation, different carcinogens (*3,4*), or promoting agents with little or no ability to initiate. For the many tissues or organs that show little or no cell proliferation at the time of exposure (liver, pancreas, urinary system including kidney and bladder, salivary glands, respiratory epithelium, central nervous system, etc.), a third property is important: the ability to induce cell proliferation, either as a direct primary mitogenic effect or a secondary regenerative effect after cytotoxic cell death (Table 2).

Initiation

Initiation has received much attention in the past 20 years. The advance in our knowledge has been very significant, even though we still do not know the fine details concerning mechanisms.

Metabolic Activation

The major advances occurred in the 1960s and early 1970s with the establishment of the need for metabolic conversion of most carcinogenic xenobiotics to highly reactive derivatives, most commonly electrophilic reactions or electrophiles (*5*). Most known carcinogens are metabolized by cytochrome P-450 mixed function oxygenase systems, localized mainly in the microsomes, but also in the nuclei. Recent research has indicated the presence of many cytochromes P-450, at least 10 or 12 and perhaps more. These cytochromes have different chemical, biochemical, and biological properties, even though there is considerable overlap between different forms. This overlap, although making trouble for the biochemist, is most appropriate when one views the need for a wide spectrum of enzyme activities to handle, physiologically, the equally wide spectrum of xenobiotics and endogenous possible substrates with which the organism is confronted.

The mixed function oxygenase cytochrome P-450 system is not the only one active in metabolizing potential carcinogens (Table 3). Reduction with DT-diaphorase (quinone reductase) (e.g., nitroflurans, nitroquinoline-*N*-oxide, nitropolycyclics, etc.); reaction with glutathione (e.g., 1,2-dibromoethane, 1,2-dichloroethane); hydrolysis with specific enzymes, such as intestinal bacterial β-glucuronidase (e.g., cycasin); and other enzymes and oxidation via the prostaglandin system or via reactive oxygen species (e.g., polycyclic aromatic hydrocarbons) are four additional known systems.

Table 2. Minimum requirements for a chemical to be a carcinogen.

Interact with tissue components, e.g., DNA
Directly
After metabolic activation
Induce cell proliferation
Directly
Via cell death
Promote—create an environment in the tissue for selective growth of initiated cells

Table 3. Metabolic generation of carcinogenic metabolites from xenobiotics.

Microsomal cytochrome P-450 system (microsomes and nuclei)
Alternate pathways, e.g., aromatic amines
Sequential or linear, e.g., polycyclic aromatic hydrocarbons
Cytosolic reductases (DT-diaphorase or quinone reductase) e.g., nitroquinone, nitroquinolines, nitrofurans and nitropolycyclics
Glutathione (with or without GSH-*S*-transferases) e.g., 1,2-dibromoethane, 1,2-dichloroethane
Prostaglandin synthesis system or reactive oxygen species e.g., polycyclic aromatic hydrocarbons
Selective enzymatic hydrolysis e.g., β-glucosidase on cycasin in intestine

In the case of the dominant system, the mixed function oxygenase system, there are some conceptual puzzles (*6*). In respect to the metabolism of the polycyclic aromatic hydrocarbons, the active derivative appears to be the same for detoxification as well as for activation for carcinogenesis. Which pathway predominates appears to be a function of the environment—diet and nutrition, other xenobiotics, etc. This view is conceptually quite acceptable. However, with aromatic amines, in which the genesis of an active carcinogenic derivative is a very minor pathway, the conceptual basis for this minor pathway seems obscure. Does this pathway have some survival value to an organism, or is it simply a necessary but useless accompaniment of the major pathways for metabolism and detoxification, the ring hydroxylation?

An exciting development has been the preparation and use of possible reactive derivatives by enzymatic or chemical procedures. Highly reactive derivatives of aromatic amines, polycyclic aromatic hydrocarbons (e.g., 7,8-dihydrodiol, 9,10-epoxide of benzo[a]pyrene) and other types of metabolites have been tested for potency as carcinogens in both *in vivo* and *in vitro* systems with many interesting findings (*7*).

In addition, studies with various inhibitors or modifiers of the metabolic activation systems have yielded significant results concerning the possible enzymatic mechanisms for activation (*7*). On the whole, these results have confirmed in a clear-cut fashion the dependence of many carcinogens for their carcinogenic efficacy on metabolic activation and conversion to reactive compounds. This phase of chemical carcinogenesis, while by no means complete, is gratifying in showing that the first step in chemical carcinogenesis is host activity relating to metabolism. The possible modulation of this first step by diet, hormones, drugs, and other xenobiotics and the correlation of these observations with the ultimate cancer development is impressive and offers models for the possible prevention of cancer in humans if the nature of the etiologic agent is known but somehow cannot be removed from the human environment.

Molecular Targets

The molecular targets for the electrophilic reactions are many—DNA, RNA, proteins, sulfhydryl groups, polysaccharides, etc. It is widely believed that the major target is DNA. As has been repeatedly shown, the DNA targets for carcinogens may be the bases themselves, the phosphate groups, or the three-dimensional structure of DNA (*8,9*). An impressive literature exists on the many details concerning the specific adducts formed, their reactivity, and possible relevance to the ultimate development of cancer and highly sensitive techniques for their measurements. Adducts at sites of H-bonding (*O*-6-alkyl guanine, *O*-4-alkyl thymine, etc.) have received the primary attention recently because of their obvious promutagenic nature. However, other lesions such as *N*-7-alkylguanine and *N*-3-alkyl adenine are known to consist of more than one form, as they show different rates of repair. These lesions are repaired by base removal, a lesion that seems equally dangerous if DNA replication occurs before the normal base is inserted.

A potentially very important development is the assessment of exposure (not risk) of humans to specific carcinogens with the use of assays for derivatives of DNA and protein adducts in blood, urine, and other tissue components or fluids. This aspect of biochemical epidemiology is discussed in detail by Curt Harris in this issue.

Oncogenes as Molecular Targets

The recent resurgence of the oncogene concept, and especially the identification of some oncogenes as related to the proliferative cell cycle (c-*fos*, c-*myc*, c-Ha-*ras*, c-Ki-*ras*, c-*myb*, P53), other oncogenes as related to known growth factors and/or growth factor receptors such as platelet derived growth factor (PDGF) and epidermal growth factor (EGF), and still other oncogenes related to the systems for signal transduction from the cell membrane have opened up many new areas in cell biology. These offer the promise of new insights into the biochemical and molecular basis for normal cell behavior. What roles they play, if any, in most carcinogenic processes remains to be critically evaluated (*10–12*). The induction of specific mutations in the c-Ha-*ras* gene by *N*-methyl-*N*-nitrosourea and by dimethylbenzathracene in the mammary gland of rats and skin of mice and in benign or malignant neoplasms in these tissues and in the same gene in mouse and rat hepatomas (*13–15*), as reviewed by Marshall Anderson in this issue, is potentially most interesting. The scientific community will await with great interest the results of critical control experiments that should aid in the decision as to whether these mutations are passive accompaniments of exposures to known mutagens such as many carcinogens, or whether they become, on activation, intimately involved mechanistically in the development of cancer. How many other genes show mutations at the same time? Why does c-Ha-*ras* seem to be the main or only oncogene affected? Does it have a much greater propensity for mutation ("hot spots")? If it is involved, what mechanistic hypotheses for its possible function in the carcinogenic process can be proposed? If it is involved, in which of the several steps [at least 8 or 9 (*16*)] is it involved and how? Answers to some of these critical questions would clarify to significant degrees at least some aspects of how cancer develops with chemical carcinogens. Critical experiments in the mammary gland, skin, and liver must include data on whether the same mutations can be found when tissue exposed to the carcinogen under initiating conditions is stimuated to undergo nonneoplastic cell proliferation such as during pregnancy in the mammary gland, nonpromoting hyperplasia in the skin, and nonneoplastic hyperplasia in the liver. True mutations would not likely be of sufficient numbers to be detectable in the original target tissue but might become detectable when the cells carrying them are amplified as in a papilloma or a nodule.

Dependence on Cell Proliferation

The major conceptual and technical advances in the metabolism of carcinogens during the first step in initiation must now enter a new phase. How does one relate these events to the biological cellular aspects of cancer development? For example, we know that while the activation of a carcinogen to a reactive derivative and the interactions of these with cellular DNA and other macromolecules are essential first steps, they are insufficient to initiate carcinogenesis. Both *in vitro* and *in vivo*, initiation does not occur unless followed by a round of cell proliferation (*16,17*). Although this is most strikingly and clearly shown in the liver (*18*) and *in vitro* (*19*), there are many indications that this may be a general phenomenon for chemical carcinogenesis and for other types of carcinogenesis (*20*). In the liver, a large number of carcinogens are activated to reactive products and these interact with DNA and other cell components. Yet most carcinogens are not carcinogenic for the liver. However, if coupled with a round of cell proliferation, many if not all of these now initiate carcinogenesis in the liver (*21,22*).

This dependence of initiation on cell proliferation has made it possible to determine whether the short-lived or long-lived adducts in DNA might be related to the initiation of carcinogenesis in the liver. With diethylnitrosamine and benzo[a]pyrene, it has been shown that only the short-lived, i.e., adducts lasting no more than 72 to 96 hr, are most relevant to the initiation of chemical carcinogenesis in the liver (*23*).

Another important feature of initiation is the repair of the relevant biochemical lesion or lesions, presumably in DNA. This topic has blossomed in the past 20 years and has established firmly that with ultraviolet light as the carcinogen for the skin, DNA repair is a major determinant in cancer development. The high incidence of both squamous cell carcinoma and malignant melanoma in patients with xeroderma pigmentosum is an experiment of nature that has given us considerable insight

into the possible role of DNA alterations in carcinogenesis.

This experience with xeroderma pigmentosum emphasizes in a major way the probable role of altered DNA in the first step in initiation of chemical carcinogenesis. Although this is often formulated in terms of mutations leading to base substitutions, the evidence for this is so far not convincing. No abnormal protein, with altered amino acid sequence, as indicative of a base substitution in the corresponding gene, has been found during initiation, with the exception of an altered c-Ha-*ras* gene in a few patients with cancer of the urinary bladder and in mammary gland in the rat after exposure to *N*-methyl-*N*-nitrosourea (*10*). In the experimental system, no evidence that the altered gene had any role to play in the carcinogenic process was provided. The immediate mutagenic effect of a mutagen was of course anticipated. Future mechanistic experimental studies may clarify this potentially exciting observation, as discussed above.

Given the newer insights into the dynamism of the mammalian genome, it is possible that carcinogenesis might be related to translocations, transpositions, gene amplifications, or other gene or DNA rearrangements rather than to a change in the base sequence. One can anticipate innovative overtures along these exciting lines in future studies on chemical carcinogenesis.

The dependence of initiation of carcinogenesis on a round of cell proliferation may indicate a need for DNA replication in order to effect the change in gene expression related to the carcinogen-induced DNA alteration. However, since the cell cycle has so many component parts in addition to DNA replication, including the activation at both the levels of gene transcription and/or gene product translation (*11,12*), it is premature to conclude that the DNA replication phase of the cell cycle phenotype is necessarily the important part in initiation.

Nature of the Initiated Cell

In any concern about mechanism, a key consideration is the nature of the initiated target cell. It is clearly evident that in no *in vivo* system studied does an initiated cell express any capacity for autonomous cell proliferation. Given the validity of this conclusion, what then is the special phenotype of initiated cells that allows them to participate in clonal expansion when the appropriate promoting environment is created?

We have a reasonable formulation in only one system, the liver. In the rat, about 100 different chemical carcinogens induce in a rare hepatocyte a resistance phenotype during initiation (*3,21,22,24–26*). This phenotype has a whole constellation of components (Table 4), including large decreases in the cytochromes P-450, cytochrome b5, and several mixed-function oxygenase activities (phase I components), and considerable increases in phase II components such as glutathione, glutathione-*S*-transferases, UDP-glucuronyl transferase I, DT-diaphorase (quinone reductase), and a special glutathione-*S*-transferase P (*27,28*). Included is a resistance to the inhibitory effects of several carcinogens including 2-acetylaminofluorene on cell proliferation, a resistance to the cytotoxic effects of the senecio alkaloid lasiocarpine and of polybrominated biphenyls (PBBs), and a resistance to the induction of fatty change (triglyceride accumulation) on feeding a choline deficient diet (*16*).

Table 4. Biochemical pattern of hepatocyte nodules for metabolizing xenobiotics.

	Decrease in	Increase in
Phase I	Cytochrome P-450 Cytochrome *b5* Several mixed-function oxidases	
Phase II		Glutathione Glutathione-*S*-transferases UDP-glucuronyl-transferase I γ-Glutamyltransferase
Other	Sulfotransferase	Epoxide hydrolase DT-diaphorase Glutathione-*S*-transferase P (P50)

This resistance enables at least some initiated hepatocytes to respond to a promoting environment that provides simultaneously a mitogenic stimulus and an inhibition of cell proliferation of the vast number of uninitiated hepatocytes. With such differential inhibition (*29*), only the few resistant initiated hepatocytes can respond to generate hepatocyte nodules very rapidly. These focal collections of altered hepatocytes undergo at least 10 to 12 cell cycles of proliferation to generate grossly visible nodules.

In the skin of mice, initiation is associated with the acquisition of resistance to terminal differentiation (*30*). Whether the resistant cells are initiated and are the precursors for papillomas and ultimately carcinomas remains to be established.

Promotion

The promoting capability of carcinogens or of noninitiating or poorly initiating promoting agents or promoters is still poorly understood.

As already indicated above, the phenotype of the initiated cell does not include any autonomous or spontaneous cell proliferation. If the initiated cells are to be expanded by cell proliferation (clonal expansion), they somehow must be stimulated or encouraged to proliferate. This can be accomplished by at least three different mechanisms: differential inhibition, differential stimulation, and differential recovery (*29*). In only one case, the rat liver, do we know that differential inhibition plays a major role in the mechanism of promotion with carcinogens (*3,21,22,24–26*). Under these conditions, the initiated cells respond to an ordinary stimulus for cell proliferation, a stimulus for regeneration. Thus, the carcinogen, by inhibiting the response of the unin-

Table 5. Biological patterns of cancer development.

	Site	Type
With discrete focal proliferations as putative precancerous steps	Skin Urinary bladder Liver Colon	Papillomas Papillomas Nodules Polyps
Without obvious focal discrete proliferations	Cervix Skin Bronchi	Atypical hyperplasia, dysplasia, carcinoma *in situ*, etc.
Without any evident precursor or precancerous lesions		e.g., acute transforming retroviral neoplasms (?)

itiated sensitive cells, the vast majority of hepatocytes, is able to indirectly select for the initiated cells. Clearly, no special receptors or altered receptors need be acquired by the initiated cells, only the ordinary ones that enable control hepatocytes to respond to many physiological or pathological mitogenic stimuli.

Perhaps this same mechanism, differential inhibition, may also apply to the skin under some circumstances (*30*), even though the nature of the stimulus is not clear. With phorbol esters as promoters, all the epidermal responsive cells, initiated and uninitated, respond. If the initiated ones show less terminal differentiation to keratin-producing cells, they could become the basis for papilloma formation by differential recovery (*29*).

These considerations apply to one group of examples of cancer development (Table 5), those in which discrete focal proliferations occur regularly. In the second group, those associated with dysplasia and carcinoma *in situ*, we have no current hypotheses for mechanisms. What is seen is an obvious disturbance in differentiation, such that the basal cells continue to proliferate and do not show normal differentiation (terminal differentiation?). The persistent papillomas, nodules, and polyps are similar in one respect; they also show a disturbance in differentiation to the mature phenotype. Whether this similarity between the patterns in groups I and II is basic is not known, despite its attractiveness as a superficial hypothesis.

With respect to the mechanism in group I, a key question is whether clonal expansion is sufficient to allow a small population of nodules, papillomas, and polyps to persist and undergo a long series of subsequent steps leading to cancer (Fig. 1). The clarification of this

A. Amplification of initiated cells ("clonal expansion") ⟶ Neoplasia

B. Amplification of initiated cells + Additional alterations in gene expression ⟶ Neoplasia

FIGURE 1. Hypotheses of promotion.

Table 6. Commonality in phenotype of preneoplastic and precancerous hepatocyte nodules.

Architecture of hepatocyte
Blood supply of nodules
Ultrastructure and organization
Biochemical pattern of handling xenobiotics
Redifferentiation (remodeling) to adult liver.

basic question will probably have to await much further insights into the many steps between the focal proliferations and cancer, the steps called collectively progression.

Agents Versus Processes

It is already evident that any hope of understanding the action of any agent, be it exogenous (carcinogen, promoter, etc.) or endogenous (a specific gene or genes), seems remote. In respect to the product of initiation-promotion, a focal proliferation, there appears to be very little relation between special properties of the agents and the tissue response. For example, in the liver, the hepatocyte nodules and their precursors, the foci or islands, are remarkably similar with a common phenotype, regardless of the varied nature of different carcinogens and promoters (*16,17,27,28*) (Table 6).

Thus, if we are to understand cancer development in any depth, and if we are to develop rational ways to prevent cancer by interrupting its development, we shall have to begin to emphasize much more the study of the fundamental cellular nature of the various steps between the nodule-papilloma-polyp and the ultimate appearance of cancer.

In this context, it may be interesting to recall the dynamic responsive nature of cells and how important this is to our eventual understanding of carcinogenesis. "The cell is the smallest integrating unit in biology: a pseudo-intelligent computer that receives, screens, changes, reacts to and adapts to a host of environmental signals. Much of this ability is apparently designed, through evolution, for cell survival and host survival" (*31*).

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REFERENCES

1. Foulds, L. Neoplastic Development, Vols. 1 and 2. Academic Press, New York, 1969 and 1975.
2. Farber, E., and Cameron, R. The sequential analysis of cancer development. Adv. Cancer Res. 35: 125–226 (1980).
3. Solt, D. B., and Farber, E. New principle for the analysis of chemical carcinogenesis. Nature 263: 702–703 (1976).
4. Tatematsu, M., Murasaki, G., Nakanishi, K., Miyata, Y., Shinohara, Y., and Ito, N. Sequential quantitative studies in hyperplastic nodules in the liver of rats treated with carcinogenic chemicals. Gann 70: 125–130 (1979).
5. Miller, E. C. Some current perspectives on chemical carcinogen-

esis in humans and experimental animals: Presidential address. Cancer Res. 38: 1479–1496 (1978).
6. Farber, E. Chemical carcinogenesis: A biologic perspective. Am. J. Pathol. 106: 270–296 (1982).
7. Conney, A. H. Induction of microsomal enzymes by foreign chemicals and carcinogenesis by polycyclic aromatic hydrocarbons: G. H. A. Clowes Memorial Lecture. Cancer Res. 42: 4875–4917 (1982).
8. Grover, P. L., Ed. Chemical Carcinogens and DNA, Vols. I and II. CRC Press, Boca Raton, FL, 1979.
9. Rajalakshmi, S., Rao, P. M., and Sarma, D. S. R. Chemical carcinogenesis: Interactions of carcinogens with nucleic acids. In: Cancer, A Comprehensive Treatise, Ed. 2, Vol. 1 (F. F. Becker, Ed.), Plenum Press, New York, 1982, pp. 335–409.
10. Barbacid, M. Oncogenes and human cancer: Cause or consequence? Carcinogenesis 7: 1037–1042 (1986).
11. Kaczmarek, L. Biology of disease: Protooncogene expression during the cell cycle. Lab. Invest. 54: 365–376 (1986).
12. Denhardt, D. T., Edwards, D. R., and Parfett, C. L. J. Gene expression during the mammalian cell cycle. Biochem. Biophys. Acta 865: 83–125 (1986).
13. Fox, T. R., and Watanabe, P. G. Detection of a cellular oncogene in spontaneous liver tumors of $B6C3F_1$ mice. Science 228: 596–597 (1985).
14. Reynolds, S. H., Stowers, S. J., Maronpot, R. P., Anderson, M. W., and Aaronson, S. A. Detection and identification of activated oncogenes in spontaneously occurring benign and malignant hepatocellular tumors of the B6C3F1 mouse. Proc. Natl. Acad. Sci. (U.S.) 83: 33–37 (1986).
15. Wiseman, R. W., Stowers, S. J., Miller, E. C., Anderson, M. W., and Miller, J. A. Activating mutations of the c-Ha-*ras* protooncogene in chemically induced hepatomas in the male B6C3F1 mouse. Proc. Natl. Acad. Sci. (U.S.) 83: 5825–5829 (1986).
16. Farber, E., and Sarma, D. S. R. Biology of disease: hepatocarcinogenesis, a dynamic cellular perspective. Lab. Invest., 56: 4–22 (1987).
17. Farber, E. Cellular biochemistry of the stepwise development of cancer with chemicals: G. H. A. Clowes Memorial Lecture. Cancer Res. 44: 5463–5474 (1984).
18. Cayama, E., Tsuda, H., Sarma, D. S. R., and Farber, E. Initiation of chemical carcinogenesis requires cell proliferation. Nature 275: 60–62 (1978).
19. Kakunaga, T. Requirement for cell proliferation in the fixation and expression of the transformed state in mouse cells treated with 4-nitroquinoline-1-oxide. Int. J. Cancer 14: 736–742 (1974).
20. Borek, C., and Sachs, L. In vitro cell transformation of x-rradiation. Nature 210: 276–278 (1966).
21. Tsuda, H., Lee, G., and Farber, E. Induction of resistant hepatocytes as a new principle for a possible short-term in vivo test for carcinogens. Cancer Res. 40: 1157–1164 (1980).
22. Tsuda, H., and Farber, E. Resistant hepatocytes as early changes in liver induced by polycyclic aromatic hydrocarbons. Int. J. Cancer. 25: 137–139 (1980).
23. Padmore, R., and Farber, E. Evidence for the transient nature of the initiating biochemical lesion using the resistant hepatocyte model. Proc. Am. Assoc. Cancer Res. 26: 117 (1985).
24. Van der Heijden, C. A., Dormans, J. A M. A., and Van Nesselrooij, J. H. J. Short-term induction of prenoeplastic nodules in the rat liver. I. The role of 2-AAF as selecting agent. Eur. J. Cancer 16: 1389–1398 (1980).
25. Van der Heijden, C. A., and Dormans, J. A. M. A. Short-term induction of neoplastic nodules in the rat liver. II. Study of their development and effects of withdrawal of 2-actylaminofluroene. Carcinogenesis 2: 147–156 (1981).
26. Leonard, T. B., Dent, J. G., Graichen, M. E., Lyght, O., and Popp, J. A. Comparison of hepatic carcinogen initiation-promotion systems. Carcinogenesis 3: 851–856 (1982).
27. Farber, E. The biochemistry of prenoeplastic liver: A common metabolic pattern in hepatocyte nodules. Can. J. Biochem. Cell Biol. 62: 486–494 (1984).
28. Roomi, M. W., Ho, R. K., Sarma, D. S. R., and Farber, E. A common biochemical pattern in preneoplastic hepatocyte nodules generated in four different models in the rat. Cancer Res. 45: 564–571 (1985).
29. Farber, E. Sequential events in chemical carcinogenesis. In: Cancer: A Comprehensive Treatise, Ed. 2, Vol. 1 (F. F. Becker, Ed.), Plenum Press, New York, 1982, pp. 485–506.
30. Hennings, H., and Yuspa, S. H. Two-stage tumor promotion in mouse skin: An alternative interpretation. JNCI 74: 735–740 (1985).
31. Farber, E. Carcinogenesis—cellular evolution as a unifying thread: Presidential address. Cancer Res. 33: 2537–2550 (1973).